

Family list

29 family members for:

EP0551849

Derived from 21 applications.

- 1 **ARYLCYCLOALKYLDERIVATE, DEREN HERSTELLUNG UND VERWENDUNGARYLCYCLOALKYLDERIVATE, DEREN HERSTELLUNG UND VERWENDUNG**
Publication info: **AT143935T T** - 1996-10-15
- 2 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **AU662382 B2** - 1995-08-31
- 3 **NOVEL ARYLCYCLOALKYL DERIVATIVES THEIR PRODUCTION AND THEIR USE**
Publication info: **AU3184793 A** - 1993-07-22
- 4 **ARYLCYCLOALKYL DERIVATIVES THEIR PRODUCTION AND THEIR USE**
Publication info: **CA2087414 A1** - 1993-07-17
CA2087414 C - 2002-04-16
- 5 **CRYOGENIC RECTIFICATION SYSTEM WITH ARGON HEAT PUMP**
Publication info: **CN1036779C C** - 1997-12-24
CN1076186 A - 1993-09-15
- 6 **ARYL CYCLOALKYL DERIVATIVES, PROCESS OF PREPARING SUCH DERIVATIVES AND THEIR USE**
Publication info: **CZ285937 B6** - 1999-12-15
CZ9204036 A3 - 1993-09-15
- 7 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **DE69305189D D1** - 1996-11-14
- 8 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **DE69305189T T2** - 1997-03-13
- 9 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **DK551849T T3** - 1997-03-10
- 10 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **EP0551849 A1** - 1993-07-21
EP0551849 B1 - 1996-10-09
- 11 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **ES2093860T T3** - 1997-01-01
- 12 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **GR3021338T T3** - 1997-01-31
- 13 **PROCESS FOR PRODUCING PHENYL CYCLOALKYL DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS COMPRISING SUCH COMPOUNDS AS ACTIVE INGREDIENT**
Publication info: **HU63598 A2** - 1993-09-28
HU221007 B1 - 2002-07-29
HU9300110D D0 - 1993-04-28
- 14 **NEW ARYLCYCLOALKYL DERIVATIVE, ITS PREPARATION AND ITS USE**
Publication info: **JP2949000B2 B2** - 1999-09-13
JP6009476 A - 1994-01-18
- 15 **Novel arylcycloalkyl derivatives their production and their use**
Publication info: **MX9300222 A1** - 1993-07-01
- 16 **ARYLCYCLOALKYL DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS BASED THEREOF**
Publication info: **RU2125553 C1** - 1999-01-27
- 17 **ARYLCYCLOALKYL DERIVATIVES, METHOD OF PREPARATION OF THESE DERIVATIVES AND THEIR USING**
Publication info: **SK280617B B6** - 2000-05-16
SK403692 A3 - 1995-03-08
- 18 **Arylcycloalkyl derivatives, their production and their use**
Publication info: **US5589514 A** - 1996-12-31
- 19 **Arylcycloalkyl derivatives, their production and their use**

Publication info: US55116911 A - 1998-07-01

20 Arylcycloalkyl derivatives, their production and their use

Publication info: US6159988 A - 2000-12-12

Data supplied from the **esp@cenet** database - Worldwide

Family list

29 family members for:

EP0551849

Derived from 21 applications.

21 Novel arylcycloalkyl derivatives their production and their use

Publication info: **ZA9300267 A** - 1993-08-23

Data supplied from the **esp@cenet** database - Worldwide



Europäisches Patentamt
European Patent Office
Office européen des brevets



⑪ Publication number:

0 551 849 A1

⑫

EUROPEAN PATENT APPLICATION

⑬ Application number: 93100279.4

⑮ Int. Cl. C07C 49/84, C07C 49/83,
C07C 49/835, A61K 31/12

⑭ Date of filing: 11.01.93

⑯ Priority: 16.01.92 EP 92100664

⑰ Date of publication of application:
21.07.93 Bulletin 93/29

⑯ Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL
PT SE

⑰ Applicant: HOECHST AKTIENGESELLSCHAFT
Postfach 80 03 20
W-6230 Frankfurt am Main 80(DE)

⑰ Inventor: Naik, Ramachandra Ganapati, Dr.
M-4, Hoechst Quarters, Darga Road
Mulund, Bombay 400 082(IN)
Inventor: Mumbaikar, Vilas Narayan, Dr.
6/44, Pratiksha Nagar
Slon (East), Bombay 400 022(IN)
Inventor: Vasumathy, Rangarejan
9-A Gulmarg

Anushakti Nagar, Bombay 400 094(IN)

Inventor: Lakdawala, Aftab Dawoodbhai, Dr.
11, Kapadia Mansion, Dr. A. Nair Road
Bombay 400 011(IN)

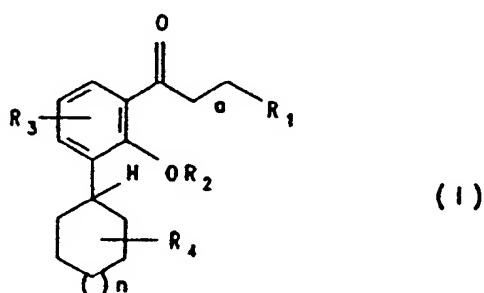
Inventor: Shirole, Mandakini Vithalrao
4/1, Brindaban, Near Shreerang Society
Thane 400 601(IN)

Inventor: Lal, Bansi, Dr.
30, Advani Apartments Mulund West
Bombay 400 082(IN)

Inventor: Blumbach, Jürgen, Dr.
Fasanenweg 8
W-6272 Niedernhausen(DE)
Inventor: Weithmann, Klaus Ulrich, Dr.
Am Domherrenwald 18
W-6238 Hofheim(DE)
Inventor: Bartlett, Robert Ryder, Dr
Schmitweg 23
W-6100 Darmstadt(DE)

⑯ Novel arylcycloalkyl derivatives their production and their use.

⑯ Compounds of formula I, wherein



EP 0 551 849 A1

the substituents R₁ - R₄ and a have the given meaning show an activity against inflammatory conditions.

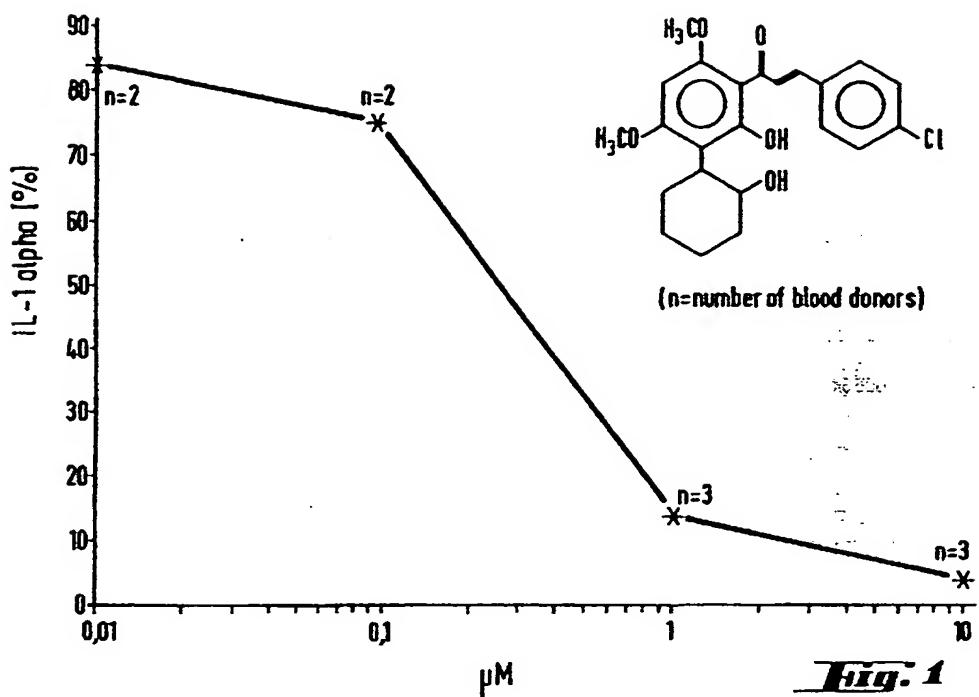
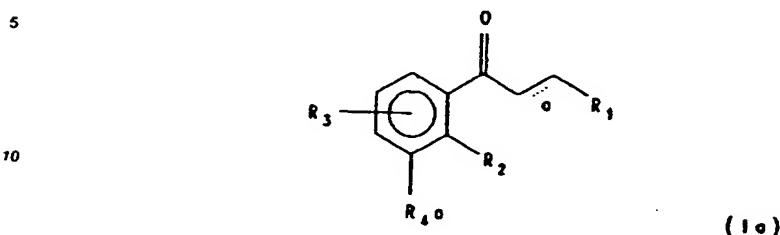


Fig. 1

The present invention relates to novel arylcycloalkyl derivatives their production and their use. The chalcones of the following general formula Ia are known by the following prior art:



1. (J.P. 87/281022) Compounds of formula Ia, wherein
 - R₁ = substituted phenyl
 - R₂ = OH
 - a = single or double bond
 - R₃ = OH
 - R_{4a} = H, isoprenyl or isopentyl
 - are effective in treatment of diseases caused by hypersecretion of androgens, e.g. prostatomegaly, alopecia in males, acne vulgaris or seborrhoea.
2. J.P. 86/026775 Compounds of formula Ia wherein
 - R₁ = substituted phenyl
 - R₂ = H, OH, acetoxy, carboxymethoxy or methoxycarbonylmethoxy
 - R₃ = OH, methoxy, benzyloxy, H
 - R_{4a} = H, isoprenyl, isopentyl
 - possess anti-hyaluronidase activity.
3. J.P. 87/142166 Compounds of formula Ia wherein
 - R₁ = substituted phenyl
 - R₂ = OH, acetoxy, carboxymethoxy, methoxycarbonylmethoxy,
 - R₃ = OH, methoxy, H
 - a = single or a double bond
 - R_{4a} = isoprenyl, isopentyl, n-propyl or H,
 - are useful as aldose reductase inhibitors - used to treat diabetic complications such as cataracts, retinitis, nerve disorder or kidney disease.
4. J.P. 86/248389 Compounds of formula Ia wherein
 - R₁ = substituted phenyl
 - R₂ = OH
 - R₃ = OH
 - a = double bond
 - R_{4a} = H
 - are useful as aldose reductase inhibitors - for treatment of diabetes mellitus complications.
5. J.P. 86/144717 Compounds of formula Ia wherein
 - R₁ = substituted phenyl
 - R₂ = H or OH
 - R₃ = H or OH
 - a = double bond
 - R_{4a} = H or OH
 - are useful as c-kinase inhibitors and antitumor agents.
6. EP 150166 Compounds of formula Ia wherein
 - R₁ = substituted phenyl
 - R₂ = H, halogen, lower alkyl, lower alkoxy, CN, carboxy, nitro,
 - R₃ = H, halogen, lower alkyl, lower alkoxy, CN, carboxy, nitro, hydroxy, substituted acetic acid derivative,
 - a = double bond
 - R_{4a} = as in R₃
 - having inhibitory effect on hydroxy-prostaglandin dehydrogenase. They may have potential local activity

against gastrointestinal disorders such as gastric ulcer, and ulcerative colitis. Other potential fields of application include the treatment of rheumatoid arthritis, circulatory disorders, cancer, lack of fertility and cell regulation.

7. J.P. 86/167288 Compounds of formula Ia wherein

5 R_1 = substituted phenyl

R_2 = H

R_3 = OH,

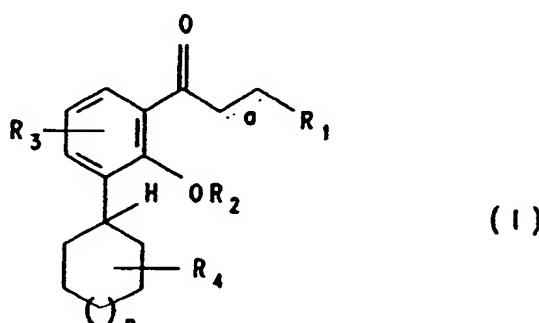
a = single bond

R_{4a} = OH

10 are selective inhibitors of 5-lipoxygenase and have excellent anti-allergic activity, thus are useful as a safe anti-allergic drug such as antiasthmatic, antiphlogistic and immune activating drug.

The present invention relates to compounds of formula I, wherein

15

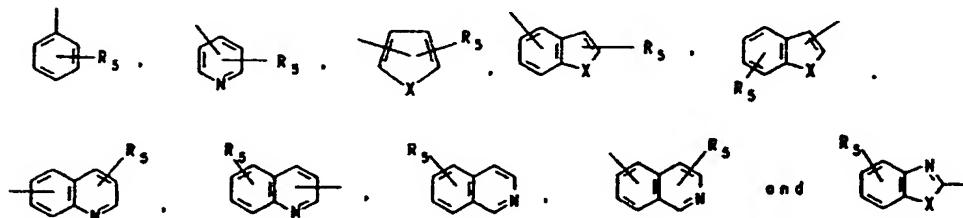


20

25

R_1 = C_1 - C_6 -alkyl, substituted C_1 - C_6 -alkyl, $C(O)O$ - C_1 - C_4 -alkyl, $C(O)OH$, or a residue selected from

30



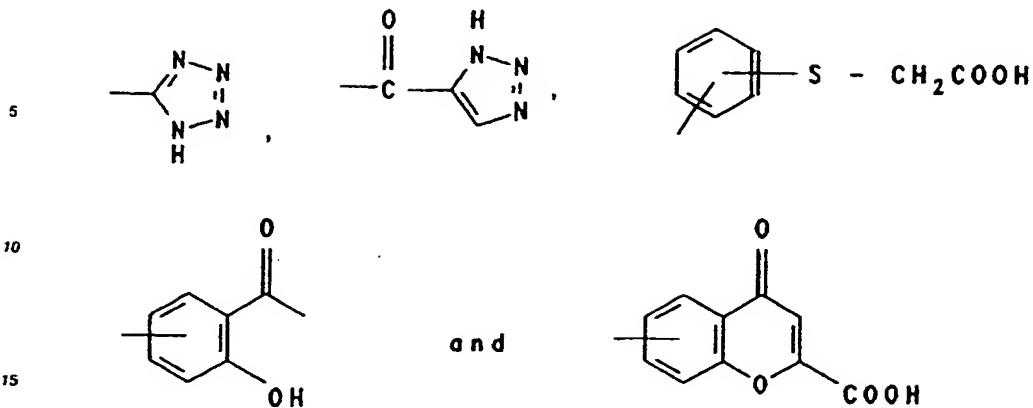
35

40

wherein R_5 is one, two, three or four of the residues which are independent from each other H, C_1 - C_6 -alkyl, substituted C_1 - C_6 -alkyl, hydroxyl, carboxyl, cyano, $-NHCO$ (O) C_1 - C_2 -alkyl, $-OC_1$ - C_2 -alkylphenyl, $-OCH_2O$, C_1 - C_6 -alkoxy, C_1 - C_4 -alkyl-O- C_1 - C_4 -alkyl, $-O-C(O)-C_1$ - C_4 -alkyl, $-C(O)-O-C_1$ - C_4 -alkyl, halogens, amino, nitro, $-NH-C_1$ - C_4 -alkyl, $-N-(C_1-C_4-alkyl)_2$, and $-C_1-C_4-alkyl-R_6$ wherein R_6 is a residue selected from

50

55



20 and

X is O, S, N-H, N-C₁-C₆-alkyl;
 R₂ is H, C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl;
 R₃ is one, two or three of the residues which are independent from each other H, C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -C(O)-O-C₁-C₆-alkyl, OH, O-C₁-C₆-alkyl, -O-C(O)-C₁-C₆-alkyl, halogen;
 R₄ is H, -OH, -O-C₁-C₆-alkyl, -O-C(O)-C₁-C₆-alkyl, -C(O)-OH, -C(O)-O-C₁-C₆-alkyl,

25

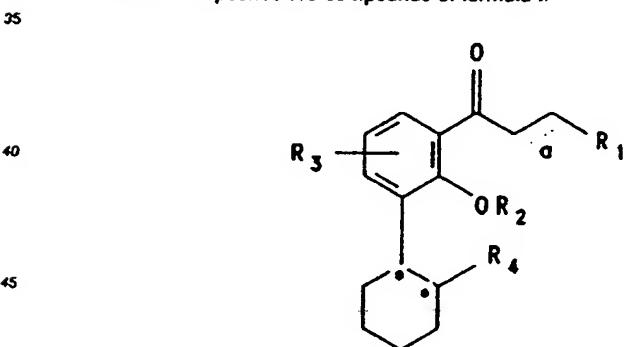
O-C(O)-C₁-C₄-alkyl-NH₂, O-C(O)-C₁-C₄-alkyl-NH-(C₁-C₄-alkyl), O-C(O)-C₁-C₄-alkyl-N-(C₁-C₄-alkyl)₂,

30

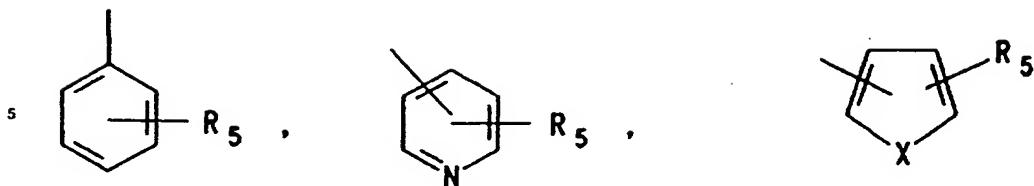
n = 0, 1 or 2 and

'a' represents an optional additional single bond.

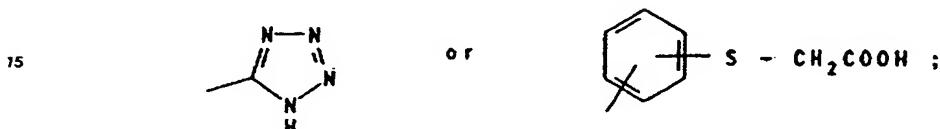
Preferred compounds are compounds of formula II



50 wherein R₁, R₂, R₃, R₄ and a are as previously defined.
 Among this group of compounds those are preferred, in which R₁ is



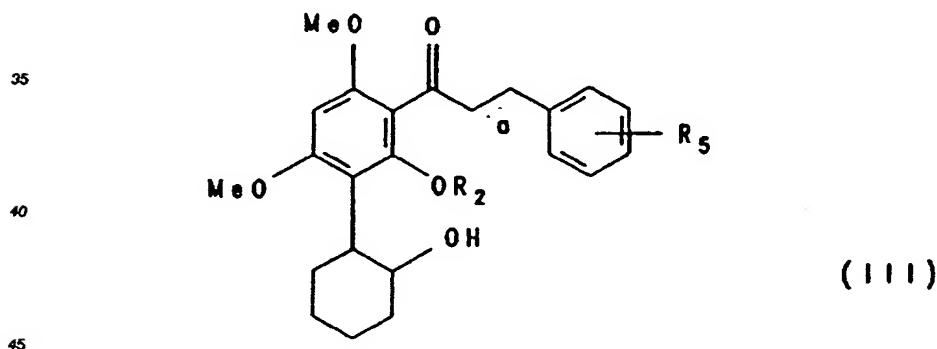
10 R₅ denoting H, C₁-C₆-alkyl, substituted C₁-C₆-alkyl, hydroxy, C₁-C₃-alkoxy, halogen, C₁-C₄-alkyl-R₆ wherein R₆ stands for



20 R₄ denotes H, OH or



30 X stands for O, NH, S, N-C₁-C₆-alkyl and a stands for an optional additional bond.
Particularly preferred are compounds of formula III



wherein
R₂ is H or C₁-C₃-alkyl,
R₅ denotes one or two halogens or one or two C₁-C₆-alkyl or C₁-C₃-alkoxy groups and a denotes an optional additional single bond.

The above term substituted alkyl, preferably C₁-C₃-alkyl, means alkyl substituted by preferably one halogen, hydroxy, C₁-C₃-alkoxy, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)-amino, carbonyl or carboxy-C₁-C₄-alkyl.

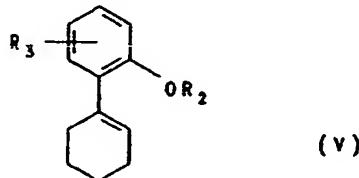
The compounds of the invention contain two asymmetric centers, designated with asterisks in formula II, at the points of attachment of R₄, (e.g. formula II, when R₄ = H) and of the aryl group on the carbocyclic ring; therefore, four isomers are possible, designated individually as the cis-(+), cis-(-), trans-(+), and trans-(-) forms. The present invention includes each of the four isomers individually or as mixtures of two or more of the four isomers.

Examples of particularly preferred compounds are:

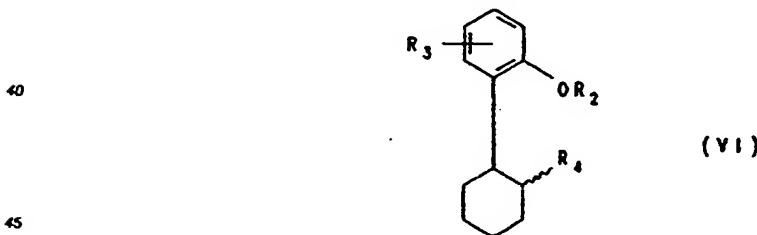
1. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(4-chlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
2. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(2-chlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
3. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-chlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
4. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(2-bromophenyl)]prop-2-enoyl]phenylcyclohexanol.
5. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-bromophenyl)]prop-2-enoyl]phenylcyclohexanol.
6. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(4-bromophenyl)]prop-2-enoyl]phenylcyclohexanol.
7. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(4-fluorophenyl)]prop-2-enoyl]phenylcyclohexanol.
8. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(2-methylphenyl)]prop-2-enoyl]phenylcyclohexanol.
9. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(4-methylphenyl)]prop-2-enoyl]phenylcyclohexanol.
10. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3,2,3-dichlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
11. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3,2,6-dichlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
12. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3,2,6-dichlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
13. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-(4-chlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
14. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-(4-chlorophenyl)]prop-2-enoyl]phenylcyclohexanol.
15. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-(3-methoxyphenyl)]prop-2-enoyl]phenylcyclohexanol.
16. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-methoxyphenyl)]prop-2-enoyl]phenylcyclohexanol.
17. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-(4-chloro-3-nitrophenyl)]prop-2-enoyl]phenylcyclohexanol.
18. trans-(+/-)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-(4-chloro-3-nitrophenyl)]prop-2-enoyl]phenylcyclohexanol.
19. trans-(+/-)-1-[4,6-Dimethoxy-2-hydroxy-3-(2-(β -amino)acetoxy) cyclohexyl]phenyl-1-(3-(3,4-dimethoxyphenyl)propanone hydrochloride.

A further subject of the instant application is a process for the production of compounds of formula I as described above wherein a compound of formula V

25



35 A) is converted into a compound of formula VI, R4 denoting OH



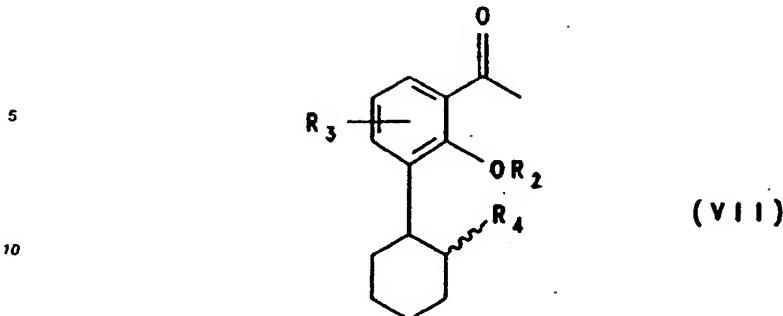
50 by treatment with a borane-solvent-complex followed by oxidation or

B) to get a compound of formula VI, a compound of formula V is treated with a peracid and the epoxide thus produced is treated with a hydride reagent or

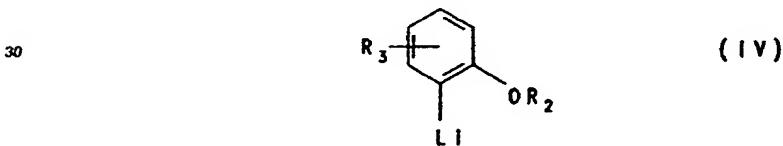
C) the compound of formula VI is produced by condensation of a suitable arene with cyclohexene oxide in the presence of an acid catalyst and

D) a compound of formula VI is treated with acetic anhydride and a mineral acid to give a compound of formula VII,

55



15 wherein R₂ is methyl and R₄ is O-C(O)-Me and
 E) a compound of formula VII as described under D) is demethylated by treatment with a Lewis acid or a demethylating agent to give a compound of formula VII R₂ denoting H and R₄ denoting OC(O)Me and
 F) a compound of formula VII R₂ denoting H and R₄ denoting OH is produced by treatment of a compound produced under E) with dilute alkali, and
 20 G) the compound of formula VII is converted into a compound of formula I (a = additional bond) by treatment with an appropriate aldehyde in the presence of a base and the compound of formula I (a = no additional bond) is produced by hydrogenation of the compound of formula I (a = additional bond), R₁, R₂ and R₃ where not explained explicitly having the meaning as indicated above.
 The compounds of formula V are prepared by methods known to a person skilled in the art. Typically
 25 they are prepared by addition of aryllithiums of formula IV to cyclohexanone followed by acid catalyzed dehydration, R₂ and R₃ having the meaning as indicated above.



35 A suitable borane-solvent complex for step A of the above sequence is for instance borane-tetrahydrofuran or borane dimethylsulfide. The oxidation can be carried out using alkaline hydrogen peroxide. A suitable peracid for step B is for instance chloroperbenzoic acid. An example for a suitable hydride reagent is lithium aluminium hydride.
 40 Step C can be carried out using as arene 1,3,5-trimethoxybenzene for example the acid catalyst being aluminium chloride.
 The mineral acid needed for step D can be for instance phosphoric acid.
 Step E can be carried out using for example as Lewis acid boron tribromide and as demethylating agent metal thiolates. The preferred dilute alkali for step F) is 2N sodium hydroxide solution.
 45 The base in the presence of which step G is carried out can be sodium hydroxide for example.
 The products according to the above reaction steps can be used for further reactions to compounds according to the instant invention. Most of said reactions can be carried out according to procedures described in European patent application 0 241 003. Additional information about starting products, intermediates and derivatization reactions can be obtained from the patent literature mentioned in the introduction.
 50 The physical constants of some of the preferred compounds of the present invention are listed in Table 1.

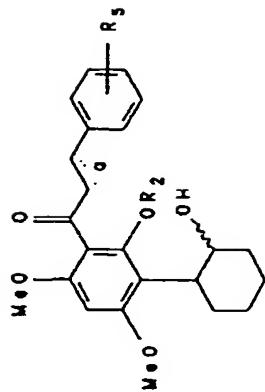
5
10
15
20
25
30
35
40
45
50

Table 1

Compound No.	R ₅	R ₂	α	m.p. °C	Sign of Rotation
1.	H	H	2',3'	183-185	+
2.	2-Cl	H		204-206	
3.	3-Cl	H		170	
4.	4-Cl	H		221	
5.	2-Br	H		203	
6.	3-Br	H		171	
7.	4-Br	H		222	

5
10
15
20
25
30
35
40
45
50
55

Compound No.	R ₆	R ₂	a	m.p. °C	Sign of Rotation
8.	4-F	H		215-216	-
9.	2,3-Cl ₂	H		216	-
10.	2,4-Cl ₂	H		226-228	-
11.	2,6-Cl ₂	H		197	-
12.	2-Me	H		199	-
13.	4-Me	H		213	-
14.	4-OMe	H		210	-
15.	4-Cl	Me		175	-
16.	4-Cl	H		190	-
17.	4-F	H		169	-
18.	3,4-Cl ₂	H		Δ2',3'	202
19.	3,5-Cl ₂	H		"	227
20.	2-OMe	H		"	215

5
10
15
20
25
30
35
40
45
50

Compound No.	R ₃	R ₂	R ₁	m.p. °C	Sign of Rotation
21.	3-OMe	H		178	-
22.	3,4-(OMe) ₂	H		194	-
23.	2,5-(OMe) ₂	H		185	-
24.	2,4-(OMe) ₂	H		224-225	-
25.	2,4,6-(OMe) ₃	H		162	-
26.	4-COOH	H		240	-
27.	4-N(CH ₃) ₂	H		187	-
28.	4-Cl, 3-NO ₂	H		215	-
29.	3-OH	H		210	-
30.	4-OH	H		210	-
31.	2-OH	H		209	-
32.	4-CF ₃	H		177	-
33.	4-NHCOCH ₃	H		274	-

55

5
10
15
20
25
30
35
40
45
50

Compound No.	R _S	R _Y	a	m.p. °C	Sign of Rotation
34.	3,4-(OMe) ₂	H	H,H	151	-
35.	2,4,6-(OMe) ₃	H	"	132	-
36.	2-OH	H	"	190	-
37.	3-OH	H	"	63	-
38.	4-OH	H	"	216	-
39.	3,4-(OH) ₂	H	"	201	-
40.	2-CH ₃	H	"	157	-
41.	3,4-(OCH ₂ Ph) ₂	H	Δ'2,3	173	-
42.	3,4-O-CH ₂ -O	H	"	185	-
43.	4-Cl	H	"	231	(+)
44.	4-Cl	H	"	231	(-)
45.	4-Cl, 3-NO ₂	H	"	235	(+)
46.	4-Cl, 3-NO ₂	H	"	235	(-)

55

5
10
15
20
25
30
35
40
45
50

Compound No.	R ₅	R ₂	a	m.p. °C	Sign of Rotation
47.	3-O-Me	H	-	191	(+)
48.	3-O-Me	H	-	191	(-)
49.	3,4-(O-Me) ₂	H	-	195	(+)
50.	3,4-(O-Me) ₂	H	-	195	(-)
51.	2,3-Cl ₂	H	-	217	(+)
52.	2,3-Cl ₂	H	-	217	(-)

55

Compounds of formula II in which $R_3 = 4,6-(OCH_3)_2$

Compound No.	R_1	R_2	R_4	m.p. °C	Sign of Rotation
1.	2-Thienyl	$\Delta 2',3'$	H	OH	179-180 (+)
2.	2-Furyl	-	H	OH	-
3.	4-Nitrophenyl	-	H	$\cdot OCOCH_3$	175
4.	4-Cyano phenyl	-	H	$\cdot OCOCH_3$	172
5.	4-Chlorophenyl	-	H	$\cdot OCOCH_2NH_2 \cdot HCl$	152
6.	3,4-Dimethoxyphenyl	-	H	$\cdot OCOCH_2NH_2 \cdot HCl$	136-138

5
10
15
20
25
30
35
40
45
50

Table 1a

The novel compounds of the present invention display interesting pharmacological activity when tested in pharmacological models; compound 4 of the above table will be used in the examples as a representative compound.

55 As shown in the examples, the instant compounds have antiinflammatory properties. The compounds are particularly useful to inhibit or antagonize the responses mediated by endogenous molecules such as lipoxygenases and/or leukotrienes, interleukins and protein kinase C. The compounds of the invention, alone

or in the form of a suitable formulation, are thus useful as medicaments in the treatment of inflammatory conditions, in particular chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis, asthma and malignancies.

Accordingly, another subject of the instant invention are the use and methods of use to treat and prevent the above-mentioned inflammatory conditions by administration of an active amount of one or more compounds of the instant invention. Furthermore, pharmaceuticals containing one or more compounds as explained above are a subject of this invention. Said pharmaceuticals can be produced and administered according to methods known in the art.

The following examples as well as the patent claims further illustrate the instant invention.

10 Example 1

Inhibition of leukotriene induced contraction of isolated guinea pig ileum.

15 Guinea pigs of either sex weighing 300-350 g were sensitized with a suspension of aluminium hydroxide gel and egg albumin. After 21 days, each animal was exposed to 0.5 % egg albumin aerosol in an air tight perspex chamber and only those animals which developed allergic bronchoconstriction were selected for further experiment.

20 The animals were tested for one week after antigenic exposure and then sacrificed by head blow and cutting carotid arteries. The lung was quickly removed and placed in aerated Tyrode solution kept at 37°C. The lung was cut into uniform strips and each strip was placed in an organ bath containing isolated guinea pig ileum connected to potentiometric recorder through isotonic transducer in the presence of Tyrode solution kept at 37°C. After stabilizing period of 30 minutes, the reactivity of ileum to histamine was confirmed by challenging it with 100 ng-200 ng/ml of histamine. The perfusion fluid was then replaced by 25 Tyrode solution containing Atropine (10^{-7} M), Mepyramine maleate (10^{-7} M) and methylsergide (10^{-7} M). Three minutes later lung strip was challenged by egg albumin (25 μ g/ml) and release of leukotrienes was monitored in terms of slow contraction of ileum. The ileum was allowed to contract for 10-15 minutes when a plateau was achieved. The test compound (compound 4 of table 1) was then added to observe the relaxation. The specificity of leukotriene antagonism was determined by inducing contraction of guinea pig 30 ileum with agonists like histamine, acetylcholine and KCl. Compounds having specific effect against lipoxygenase products induced contraction normally would not show any inhibition of histamine, acetylcholine and KCl induced contraction. The data are shown in table 2.

Table 2

Effect of Compound No. 4 on isolated guinea pig ileum precontracted with leukotrienes		
Conc. (M)	% Relaxation	App. IC ₅₀ (M)
1.2 X 10 ⁻⁶	36.8	
1.68 X 10 ⁻⁶	50.5	1.68 X 10 ⁻⁶
2.4 X 10 ⁻⁶	62.4	
7.2 X 10 ⁻⁶	68.0	

45 No effect on histamine and KCl induced contraction up to 7.11×10^{-5} M.

Compound 4 as representative of the novel compounds of the present invention inhibits the contractions induced by leukotrienes.

50 Example 2

Inhibition of Cotton Pellet Granuloma in Rats:

This model permits the evaluation of a compound's potential to inhibit artificially induced granuloma. The implantation of carrageenin impregnated cotton pellets results in production of large well defined 55 granuloma which are easily dissected. The potency of the compounds are assessed by measuring the reduction in granuloma tissue formation.

Preparation of Saline and Carrageenin Cotton Pellets:

5 Cotton wool pellets weighing 40 mg were used for sterilization. Half the number of pellets were dipped in saline and the remaining in 1 % aqueous solution (Viscarin® type 402, Marine Colloids Inc. Springfield) till they were soaked well, squeezed slightly to remove excess saline or carrageenin.

10 Pellets were dried overnight under a lamp. The pellets in the weight range of 42-44 mg were selected.

Animal Preparation:

15 Rats (in groups of 6, male or female, Charles River, Wistar, weighing 140-150 g) were anaesthetized with ether. The back was shaved and cleaned; swabbed with alcohol and one centimeter incision was made in the lower midback. A small channel was made bilaterally using a blunt forceps and one cotton pellet placed in each channel. Air from the incision was removed and the wound was stitched. The test compound was prepared in 0.5 % carboxy methyl cellulose and was administered orally at a dose of 10, 20 and 30 mg/kg daily for seven days. Three hours after the administration of the last dose on day 7, animals were sacrificed.

20 The pellets were removed by cutting the skin along the dorsal midline and peeling the skin away from the bodywall in both lateral directions. The pellets were weighed and then placed in drying oven at 140 °C overnight. The dry weights were then recorded and the amount of granuloma was assessed by subtracting the original pellet weight from wet weights and dry weights. The data was evaluated using the difference of left and right weights (cf. table 3).

Table 3

Effect of Compound No. 4 on Cotton Pellet Granuloma in Rats.			
Treatment	Dose mg/kg, p.o. X 5	% Inhibition of granuloma	
		Wet wt.	Dry wt.
Compound No. 4	10	21	35.6
	20	54	89.0
	30	64	82.8
Hydrocortisone	30	20.5	37.5

35 Compound 4 as representative of the compounds of the present invention inhibit the granuloma formation induced by carrageenin.

Example 3

40 Inhibition of Micro-anaphylactic shock of Guinea Pigs:

Guinea pigs of either sex weighing between 300-350 g were sensitized with egg albumin absorbed over Al(OH)₃ gel. After 21 days of sensitization, each animal was placed in an air tight perspex chamber and exposed to 0.5 % egg albumin aerosol through EEL atomizer. EEL atomizer was operated by connecting it to the pressurized air through water trap and dial type sphygmomanometer at the constant air pressure of 180 mm Hg. The time of onset of asthma in seconds and recovery period in minutes was noted.

45 Each animal was exposed to egg albumin aerosol at an interval of 15 days to maintain the consistency of the reactivity of animals to the antigen. After 3 such control exposures, animals were subjected to drug treatment. On the day of experiment one group of Guinea pig consisting of 10 animals was kept as control exposing them only to 0.5 % egg albumin aerosol. Another group of 10 guinea pigs was treated with Indomethacin 10 mg/kg i.p. 30 mins. before the exposure to the antigen. Yet another group of 10 guinea pigs was pretreated with Indomethacin 10 mg/kg i.p. and 30 mins after Indomethacin pretreatment the test compound (20 mg/i.p.) was injected. Fifteen mins after the administration of the test compound the animals 50 were exposed to 0.5 % egg albumin aerosol. Onset time of recovery period of each group was noted (cf. table 4).

Table 4

Effect of Compound No. 4 on microanaphylactic shock of guinea pigs			
	Treatment	Onset Time in secs.	Recovery period in mins.
5	Control group	75 + 8.7	37 + 3.4
10	Indomethacin treated group 10 mg/kg, i.p.	82.4 + 11.5	147.8 + 3.5
15	Compound 4, 20 mg/kg ⁻¹ , i.p. present invention + pretreatment with indomethacin, 10 mg/kg, i.p.	149.2 + 25.1	77.8 + 4.7

Compound 4 as the representative example of the novel compounds of the present invention protects the animals from bronchoconstriction induced by leukotrienes, subsequent to the exposure to egg albumin aerosol.

Example 4

Inhibition of IL-1 release human mononuclear cells:

20 Purification of mononuclear cells from human blood.

10 ml of human blood are carefully drawn from the antecubital vein using a syringe containing 1 ml of a solution of 3.8 % sodium citrate. After dilution with 10 ml PM 16 (Serva, Heidelberg, FRG) and underlayering with 15 ml Lymphoprep® (Molter GmbH), the sample is centrifuged at 400 X g for 40 min at 20 °C.

25 The mononuclear cells forming a white ring between lymphoprep and plasma are carefully aspirated by a syringe, diluted with 1:1 with PM 16 and centrifuged again at 400 X g for 10 min. The supernatant is washed with 10 ml RPMI 1640 (Gibco, Berlin, FRG), containing additionally 300 mg/l L-glutamine, 25 mmol/l RPMI 1640, containing additionally 300 mg/l L-glutamine, 25 mmol/l HEPES, 100 µg/ml streptomycin and 100 µg/ml penicillin. Finally, using a coulter counter IT the cell suspension is adjusted to 5 X 10⁶ cells/ml. The cells consist of approx. 90 % lymphocytes and 10 % monocytes.

Stimulation of Interleukin 1 from human mononuclear cells in vitro:

30 10 µl DMSO/water (1:10, v/v), containing the test compound, is added to 480 µl of a suspension, containing 5 X 10⁶ mononuclear cells. The synthesis of IL-1 is stimulated by the addition of 10 µl DMSO/water (1:10, v/v), containing 0.5 µg LPS (Salmonella abortus equi, Sigma). After incubation at 37 °C for 18 hours the samples are cooled to 0 °C and centrifuged for 1 min in a table centrifuge. 25 µl aliquots of the supernatant are assayed for IL-1 alpha activity using a commercially available 125-I-IL-1-alpha radioimmunoassay Kit (Amersham/UK), and for IL-1 beta in a similar way using the specific test kit. Control experiments are performed as described without test compound, or with cycloheximide as a test compound.

40 The effect of compound 4 as inhibitor of LPS stimulated IL-1 alpha (Approx. IC₅₀ = 200 - 300 nmol/l), is shown in Fig. 1

Compound 4 as representative example of the compounds of the present invention inhibits LPS stimulated IL-1 alpha release from human mononuclear cells in vitro.

45 Compounds of the instant application are prepared as described below:

Example 5

Preparation of 1-(2,4,6-Trimethoxyphenyl)cyclohexene:

50 An example of formula V where in R₃ = 4,6-dimethoxy, R₂ = CH₃.

2,4,6-Trimethoxybromobenzene (1 eqvt) is taken in a flame dried 3 - necked flask under nitrogen. Dry tetrahydrofuran (THF) (983 ml) is added and the reaction mixture is cooled to -30 °C. n-BuLi (1.3 eqvt.) in hexane (commercial) is added dropwise and after the addition the reaction mixture is stirred for 30 min. Thin layer chromatographic examination at this stage indicates completion of metallation reaction. Cyclohexanone (1.1 eqvt) diluted with equal volume of dry THF is added to the reaction mixture at -30 °C and the reaction mixture stirred for another one hour at -30 °C and later allowed to come to room temperature. Water

(150 ml) was added and extracted with ethyl acetate. The ethyl acetate layer is dried over anhydrous sodium sulfate and concentrated. The residue is taken in dichloromethane and stirred for 30 min with catalytic amount of p-toluenesulfonic acid (0 g). the dichloromethane layer is washed with sodium bicarbonate solution followed by water and dried. The residue was crystallised from Disopropylether to give the title compound, m.p. 127 °C, Yield: 64.7 %.

Example 6

Preparation of *trans*-(\pm)-2-(2,4,6-Trimethoxyphenyl)cyclohexanol:
an example of formula VI where in $R_2 = CH_3$, $R_3 = 4,6$ -dimethoxy and $R_4 = OH$.

A compound of formula V (from example I) (1 eqvt.) is taken along with sodium borohydride (4 eqvt.) and dry THF (2,200 ml). The reaction mixture is cooled to 0 °C under nitrogen and borontrifluoride etherate (5.1 eqvt.) was added dropwise. After the addition is complete, the temperature is raised to 50 °C and stirred for 30 min. The reaction mixture is cooled to room temperature and water is added dropwise to destroy excess diborane. The organoborane is oxidised by simultaneous addition of 30 % H_2O_2 (248 ml) and 3 M NaOH (248 ml) solution. After the addition the reaction mixture is heated at 50 °C for 3 hours. After completion of oxidation, the reaction mixture is diluted with water and extracted with ethyl acetate. The ethyl acetate layer is dried and concentrated. The crude product is purified by flash chromatography on silica gel using 10 % ethyl acetate in pet. ether, mp 123 °C, yield: 52 %.

Example 7

Preparation of *trans*-(\pm)-1-[3-(2-Acetoxy)cyclohexyl-2,4,6-trimethoxy]phenyl-1-ethanone: Formula VII where in $R_3 = 4,6$ -dimethoxy, $R_2 = CH_3$ and $R_4 = O-CO-CH_3$.

The product from example II (1 eqvt.) is taken in dry methylene chloride (1520 ml). Acetic anhydride (25 eqvt) and phosphoric acid (152 ml) is added and stirred at room temperature for one hour. The reaction mixture is worked up by adding sodium carbonate solution till the reaction mixture is alkaline and extracted with dichloromethane. The organic layer is thoroughly washed with water and dried. The crude product after removal of the solvent is crystallised from pet.ether. mp 87 °C, yield: 84 %.

Example 8

Preparation of *trans*-(\pm)-1-[3-(2-Acetoxy)cyclohexyl-4,6-dimethoxy-2-hydroxy]phenyl-1-ethanone: Formula VII where in $R_2 = H$, $R_3 = 4,6$ -dimethoxy und $R_4 = O-CO-CH_3$.

The product from example III (1 eqvt) is taken in dry dichloromethane (5,450 ml) and cooled to 0 °C. Borontribromide (1.1 eqvt) is added with a syringe and stirred at 0 °C for one hour. Water is added carefully and the product is extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate. The crude product is crystallised from ethyl acetate, mp 151 °C, yield: 70-71 %.

Example 9

Preparation of *trans*-(\pm)-2-[3-Acetyl-4,6-dimethoxy-2-hydroxy]phenylcyclohexanol: Formula VII where in $R_2 = H$, $R_3 = 4,6$ -dimethoxy, $R_4 = OH$.

The product from Example IV (1 eqvt.) is stirred under nitrogen atmosphere with methanolic potassium hydroxide solution (20 eqvt.), MeOH:water:3:1) for six hours. The reaction mixture is acidified with dil HCl and the precipitate is filtered off, washed, dried and crystallised from ethylacetate, mp 161 °C, yield: 88-89 %.

Example 10

Preparation of *trans*-(\pm)-2-[4,6-Dimethoxy-2-hydroxy-3-(3-(4-chlorophenyl)prop-2-(E)-enoyl)]-phenylcyclohexanol: Formula II where in $R_1 = 4$ -chlorophenyl, a = another bond $R_2 = H$, $R_3 = 4,6$ -dimethoxy and $R_4 = OH$.

The product from example V (1 eqvt.) is stirred with 4-chlorobenzaldehyde (3 eqvt.) and 10 % alcoholic sodium hydroxide (30 eqvt.) at room temperature for 24 hours. The reaction mixture is acidified with dil HCl at 0°C to pH 5 and the orange precipitate is collected by filtration. Recrystallised from ethyl alcohol, mp 221°C, yield: 68 %.

5

Example 11

Preparation of *trans*-(\pm)-2-[4,6-Dimethoxy-2-hydroxy-3-(4-chlorophenyl)propanoyl]phenylcyclohexanol: Formula II where in R₁ = 4-chlorophenyl, a = no bond, R₂ = H, R₃ = 4,6-dimethoxy and R₄ = OH.

10

The product from example VI is stirred with 10 % pd/c (5 mol %) in ethyl alcohol and under hydrogen overnight. The catalyst is filtered off and the solvent concentrated to give the product, mp 190°C, yield: 90 %.

15

Example 12

An alternative preparation of *trans*-(\pm)-2-[2,4,6-trimethoxy)phenylcyclohexanol: Formula VI where in R₂ = CH₃, R₃ = 4,6-dimethoxy and R₄ = OH.

20

2,4,6-Trimethoxybenzene (1 eqvt.), cyclohexene oxide (1.5 eqvt.) and dry dichloromethane (840 ml) are taken in 3-necked r.b flask equiped with a stirrer. The reaction mixture is cooled to -78°C and aluminium chloride (1.5 eqvt.) is added in small portion over a period of one hour. The stirring was continued for an additional period of three hours. The reaction mixture is worked up by addition of water and extracted with ethyl acetate. The crude product is crystallised from petroleum ether, mp. 123°C, yield: 63-64 %.

25

Example 13

Resolution of (\pm)-*trans*-2-(2,4,6-trimethoxy)phenylcyclohexanol: a compound of formula VI wherein R₂ = H, R₃ = 4,6-dimethoxy und R₄ = OH.

30

(\pm)*trans*-2-(2,4,6-trimethoxy)phenylcyclohexanol (50.0 g; 0.18797 mol), 3-nitrophthalic anhydride (26.299 g; 0.18797 mol) and pyridine (42.18 ml; 2.78x0.18797 mol) are heated at 100°C under N₂ atmosphere for 3h. Reaction mixture is cooled to 0°C, neutralised with 2N HCl and the product obtained extracted with chloroform. The residue after evaporation of solvent is crystallised from methanol (400 ml) to give the

35 crystals of compound of the formula VI, wherein R₄ is 3-nitrophthaloyloxy (59.0 g; mp. 198-200°C). The hemi acid (0.1285 mol) is treated with (\pm)cinchonine (37.85 g; 0.1285 mol) in methanol (250 ml) on steam bath for 30 minutes. Solvent removed at the reduced pressure and the residual salt [96.5 g, OR (+) 84.75° (Hg, 578)] crystallised from ethyl acetate-petether (1:1 1400 ml) to afford the crystals (45.0 g; OR (+) 75.11° (Hg, 578) and another liquor [50.0 g; OR (+) 97.30° (Hg, 578)].

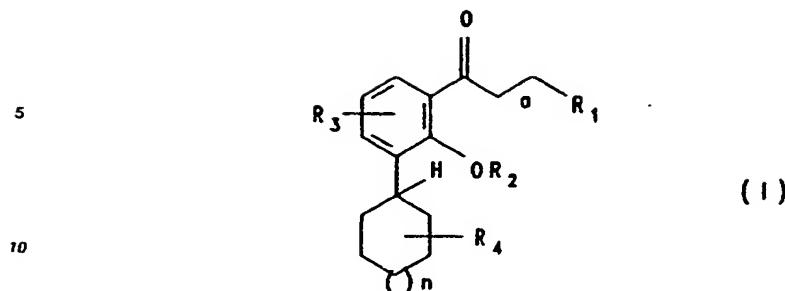
40 The crystals (45.0 g) on further crystallisations (thrice) from ethyl acetate-petether afford enriched cinchonine salt [31.0 g OR (+) 71.08° (Hg, 578)]. The enriched salt on treatment with 2N HCl at 0° gives the resolved (-) compound of the formula VI, wherein R₄ is 3-nitrophthaloyloxy [16.1 g; OR (-) 37.15° (Hg, 578)]. The hemi acid on hydrolysis with 7.5 % KOH solution in methanol - water (1:2; 587 ml) at reflux temperature, followed by crystallisation of the product from ethyl acetate - pet ether (24:160 ml) yield (-) 45 -*trans*-2-(2,4,6-trimethoxy)phenylcyclohexanol [7.0 g; OR (-) 43.430 (Hg, 578)].

45 The mother liquor (50.0 g) is treated with 2N HCl at 0° and the product is subjected to crystallisations (thrice) from ethyl acetate-pet ether to give the crystals of the resolved (+) compound of the formula VI; wherein R₄ is 3-nitrophthaloyloxy [15.1 g; OR (+) 35.65° (Hg, 578)]. The hemi acid on hydrolysis with 7.5 % KOH solution in methanol-water (1:2; 548.5 ml) at reflux temperature for 60h followed by crystallisation of

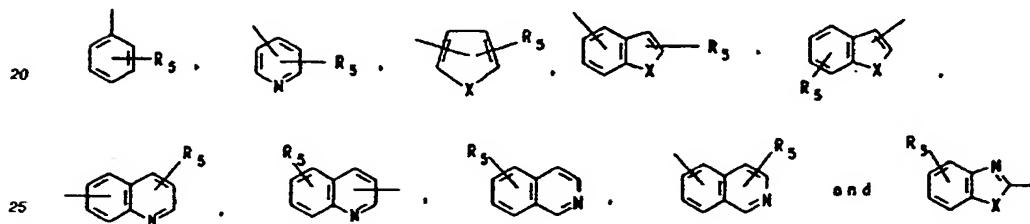
50 the product from ethyl acetate-pet ether (25:150 ml) yields (+) *trans*-2-(2,4,6-trimethoxy)phenylcyclohexanol [7.24 g; OR (+) 42.30° (Hg, 578)].

Claims

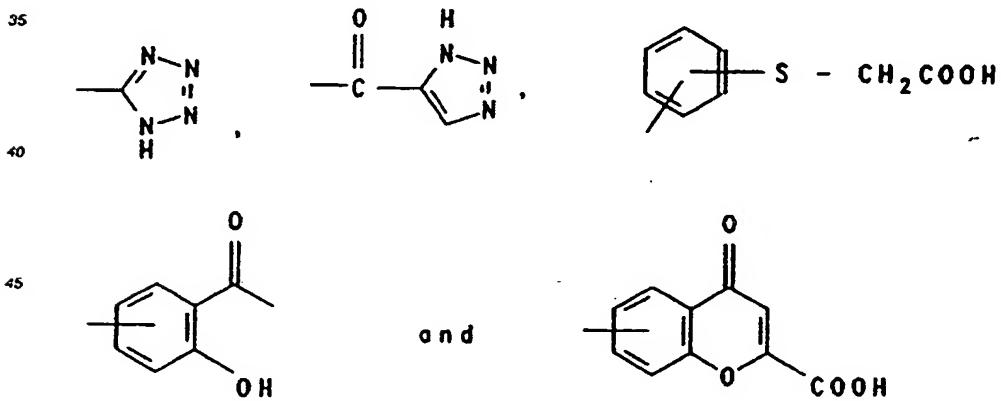
55 1. Compounds of formula I



15 wherein
R₁ denotes C₁-C₆-alkyl, substituted C₁-C₆-alkyl, C(O)O-C₁-C₄-alkyl, C(O)OH, or a residue selected from



35 wherein R₅ is one, two, three or four of the residues which are independent from each other H, C₁-C₆-alkyl, substituted C₁-C₆-alkyl, hydroxy, carboxy, cyano, -NHC(O)C₁-C₃-alkyl, -OC₁-C₃-alkylphenyl, -O-CH₂-O-, C₁-C₆-alkoxy, C₁-C₄-alkyl-O-C₁-C₄-alkyl, -O-C(O)-C₁-C₄-alkyl, -C(O)-O-C₁-C₄-alkyl, halogens, amino, nitro, -NH-C₁-C₄-alkyl, -N-(C₁-C₄-alkyl)₂, and -C₁-C₄-alkyl-R₆ wherein R₆ is a residue selected from



55 and

X is O, S, N-H, N-C₁-C₆-alkyl;

R₂ is H, C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl;

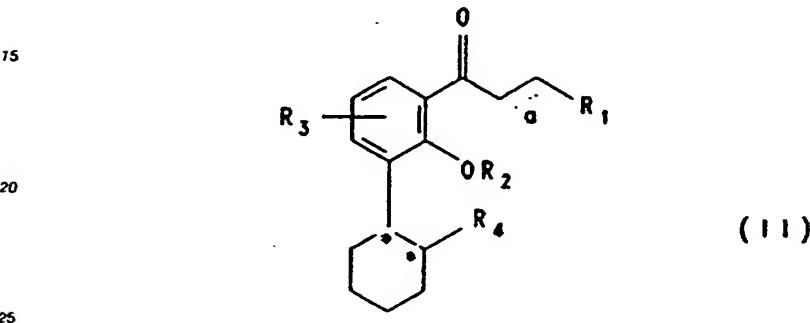
R₃ is one, two or three of the residues which are independent from each other H, C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -C(O)-O-C₁-C₆-alkyl, OH, O-C₁-C₆-alkyl, -O-C(O)-C₁-C₆-alkyl, halogen;

R₄ is H, -OH, -O-C₁-C₆-alkyl, -O-C(O)-C₁-C₆-alkyl, -C(O)-OH, -C(O)-O-C₁-C₆-alkyl.

5 $O-C(C_1-C_4\text{-alkyl})-NH_2$, $O-C(C_1-C_4\text{-alkyl})-NH-(C_1-C_4\text{-alkyl})$, $O-C(C_1-C_4\text{-alkyl})-$
 N-($C_1-C_4\text{-alkyl}$)₂,

10 $n = 0, 1$ or 2 and
 'a' represents an optional additional single bond.

15 2. Compounds as claimed in claim 1, wherein said compounds have the formula



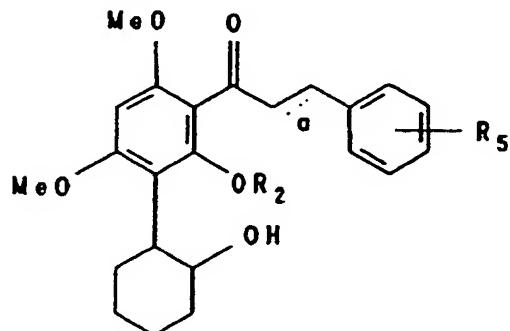
X stands for O, NH, S, N-C₁-C₆-alkyl and a stands for an optional additional bond.

4. Compounds as claimed in one or more of claims 1 - 3 wherein said compounds have the formula III

5

10

15



(III)

20 wherein

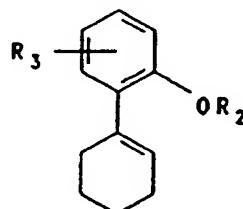
R2 is H or C₁-C₃-alkyl,

R5 denotes one or two halogens or one or two C₁-C₆-alkyl or C₁-C₃-alkoxy groups and a denotes an optional additional single bond.

25 5. A process for the production of compounds as claimed in claim 1 wherein a compound of formula V

30

35



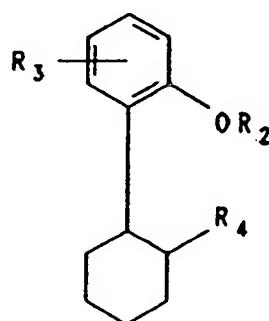
(V)

A) is converted into a compound of formula VI, R4 denoting OH

40

45

50



(VI)

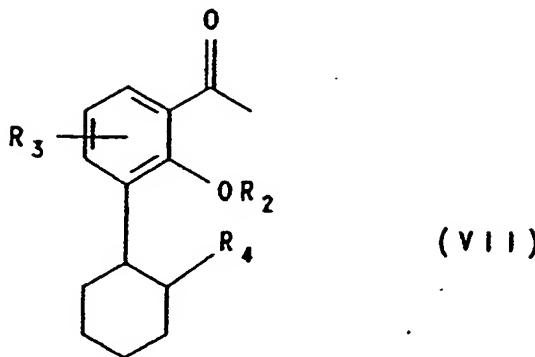
55 by treatment with a borane-solvent-complex followed by oxidation or
 B) to get a compound of formula VI a compound of formula V is treated with a peracid and the epoxide thus produced is treated with a hydride reagent or
 C) the compound of formula VI is produced by condensation of a suitable arene with cyclohexene oxide in the presence of an acid catalyst and

D) a compound of formula VI is treated with acetic anhydride and a mineral acid to give a compound of formula VII.

5

10

75



20 wherein R₂ is methyl and R₄ is O-C(O)-Me and
 E) a compound of formula VII as described under D) is demethylated by treatment with a Lewis acid or a demethylating agent to give a compound of formula VII R₂ denoting H and R₄ denoting OC(O)-Me and
 F) a compound of formula VII R₂ denoting H and R₄ denoting OH is produced by treatment of a compound produced under E) with dilute alkali, and
 G) the compound of formula VII is converted into a compound of formula I (a = additional bond) by treatment with an appropriate aldehyde in the presence of a base and the compound of formula I (a = no additional bond) is produced by hydrogenation of the compound of formula I (a = additional bond), R₁, R₂ and R₃ where not explained explicitly having the meaning as defined in claim 1.

30 6. A pharmaceutical containing an active amount of at least one compound as claimed in claims 1 - 4.

35 7. The use of compounds as claimed in one or more of claims 1 - 4 for the prevention and/or treatment of inflammatory conditions, in particular chronic inflammatory conditions.

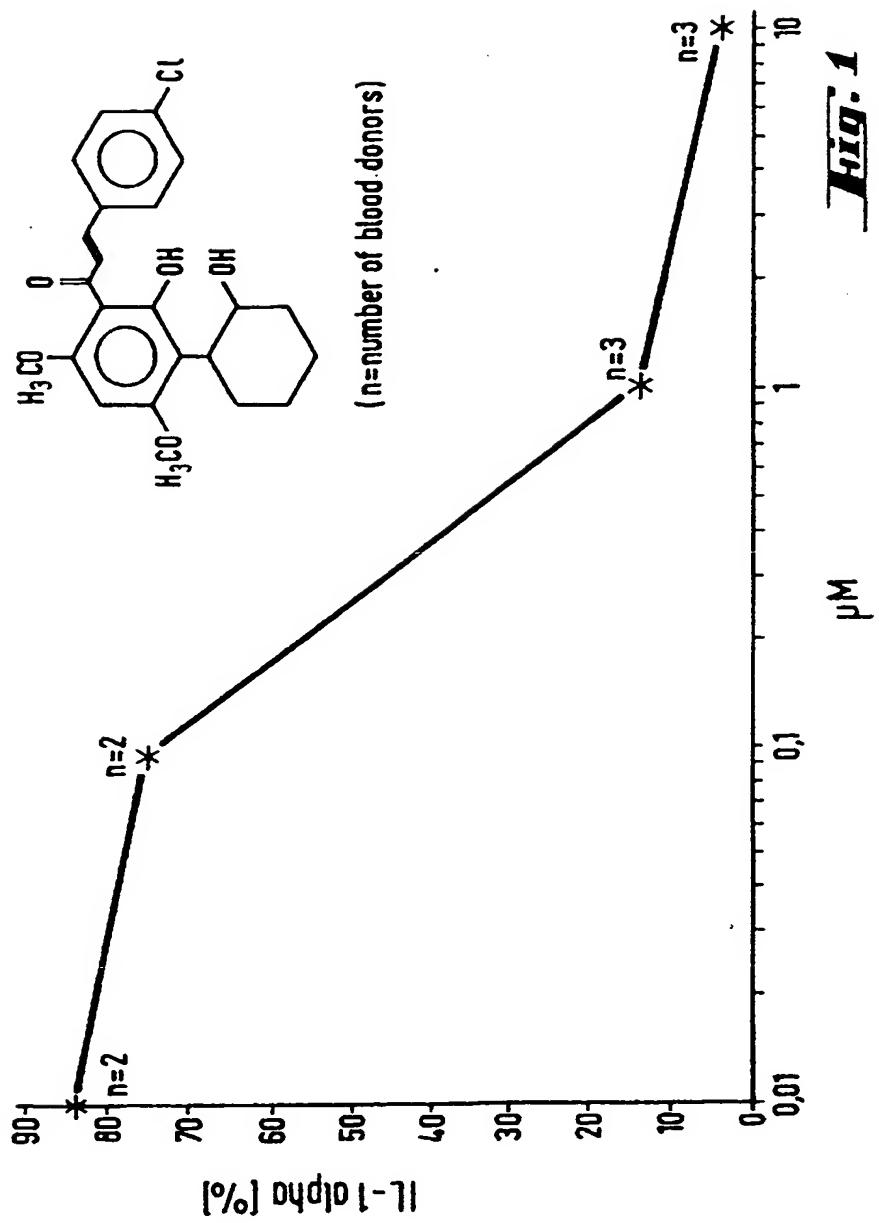
40 8. The use of compounds as claimed in one or more of claims 1 - 4 for the production of pharmaceuticals having an action against inflammatory conditions, in particular against chronic inflammatory conditions.

45 9. A process for the production of pharmaceuticals as claimed in claim 6, wherein one or more compounds as claimed in claims 1 - 4 are, optionally together with pharmaceutical auxiliaries and/or excipients, brought into a suitable administration form.

45

50

55





European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

EP 93 10 0279

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
Category	Citation of document with indication, where appropriate, of relevant passage	Relevant to claim	
A	EP-A-0 292 576 (TSUMURA JUNTENDO, INC.) * claims * -----	1,6	C07C49/84 C07C49/83 C07C49/835 A61K31/12
A	FR-A-2 602 228 (S. KIRKIACHARIAN) * page 1 * -----	1,6	
A	DE-A-2 616 479 (DR. KARL THOMAE GMBH) * page 21; claim 1 * -----	1,6	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
			C07C A61K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a technological search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p>			
<p>see sheet C</p>			
Place of search THE HAGUE	Date of completion of the search 06 APRIL 1993	BONNEVALLE E.I.	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <hr/> <p>A : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			



EP 93 10 0279 -C-

INCOMPLETE SEARCH

Claims searched completely : 4,6-9
Claims searched incompletely : 1-3,5

Reason : As the drafting of the claims is not clear and concise (art. 83-84 EPO) and encompassed such an enormous amount of products, a complete search is not possible on economic grounds (See guidelines for examination in the EPO, part B, Chapter III,2). So the search has been limited (Rule 45) to the example).

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.